PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	30.06.2004
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
JPP184	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00989	07.03.2003	07.03.2002

Applicant
ROYAL HOLLOWAY UNIVERSITY OF LONDON, et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JPP184	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 03/00989	International filing date *(day/month/year)* 07.03.2003	Priority date *(day/month/year)* 07.03.2002
International Patent Classification (IPC) or both national classification and IPC C12N3/00		
Applicant ROYAL HOLLOWAY UNIVERSITY OF LONDON, et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.10.2003	30.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bulcao de Melo Barre Telephone No. +49 89 2399-8972

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00989

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-16 received on 21.05.2004 with letter of 20.05.2004

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 17

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	15 (No Assessment, see item 5.2)

2. Citations and explanations

see separate sheet

SECTION I

1. The amended **claims 1-16** filed with your letter of 20.05.04 are considered to be allowable under **Article 34 (2) (b) PCT**.

SECTION V

2. Reference is made to the following documents:

D1: Journal of Bacteriology, Vol. 183, No. 21, 2001, pages 6294-6301
D2: WO 02 00232

3. Novelty (**Article 33(2) PCT**)

The present application does not satisfy the criterion set forth in **Article 33 (2) PCT** because the subject-matter of **claims 1-16** is considered to be part of the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

3.1. The Applicant attention's is drawn to the fact that "first medical use" formulation for product claims is recognized only in some contracting states.
Moreover, the following should be considered.
"First medical use" claims are directed to products, which are known *per se* in the prior art, limited for a specific medical use, provided that the known product was not previously disclosed for use in surgery, therapy or diagnostic methods practised in the human or animal body.
A claim to a known product for the first use in surgical, therapeutic and/or diagnostic methods should be in a form such as: "*product X*" followed by the indication of the use, for instance"...*as an antibacterial agent*" or "...*for curing disease Y*".
These type of claims will be regarded as restricted to the product when presented or packaged for the use. The administration route of the product has therefore no limitation in the scope of a "first medical use" claim.

In the present case, the spores of the present application are known in the prior art and their use in therapy has been previously disclosed (see items 3.2 and 3.3).
Therefore, in the present case, a "first medical use" claim format is not allowable.

3.2. Document **D1** discloses recombinant *Bacillus subtilis* spores expressing an antigen, tetanus toxin fragment C (TTFC), as a fusion protein with a spore coat protein, CotB. The strategy to obtain said recombinant spores was based on the use of the *cot*B gene and of its promoter, the cloning of the antigen (*tet*C) in frame to either the 3' (fusion A, clone RH103) or 5' (fusion B) end of the *cot*B for the construction of translation fusions, the chromosomal integration of the *cot*B-*tet*C gene fusions into the coding sequence of the nonessential gene *amy*E by double-crossover recombination, the transformation of vegetative cells with said fusion constructs, induction of sporulation of the transformed cells and isolation and purification of the resulting spores.
Recombinant spores of strain RH103 (carrying fusion A) were used for the immunization of mice, resulting in high levels of TTFC-specific IgG antibodies compared to mice immunized with wild-type spores.

(See Abstract; Materials and Methods; page 6297, left hand column; page 6299, paragraph bridging left and right hand column, Discussion and figure 1).

Therefore, the subject-mater of **claims 1-7, 9, 15 and 16** is not novel over **D1**.

3.3. Document **D2** discloses recombinant *Bacillus subtilis* spores expressing an antigen as a fusion protein with a spore coat protein (such as CotA, CotB, CotC, CotD...). The fusion construct, which is obtained by using the spore coat protein promoter and ligating the antigen to the 3' end of the spore coat protein, is introduced into a host strain which is induced to sporulate. The resulting recombinant spores are isolated therefrom. Some recombinant spores are rendered non-viable, i.e. do not germinate. The recombinant spores are used to vaccinated mice. The administration of the spores, performed orally or intra-nasally, induces an immune response.
D2 discloses several applications of the recombinant spores, namely as therapeutic and prophylactic agents, pharmaceutical compositions and vaccines, for modulating an immune response. Said compositions comprise a recombinant spore or at least two different spores and a pharmaceutical acceptable excipient or carrier.
(See Abstract; examples and claims).

Therefore, the subject-mater of **claims 1-5 and 7-16** is not novel over **D2**.

4. Inventive Step (**Article 33(3) PCT**)

Regarding that the subject-matter of **claims 1-16** is not novel, it also does not involve an inventive step.

5. Industrial Applicability (**Article 33(4) PCT**)

5.1. The subject-matter of present **claims 1-14 and 16** is susceptible of industrial applicability as defined in **Article 33 (4) PCT**.

5.2. For the assessment of the present **claim 15** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in document **D2** is not mentioned in the description, nor is this document identified therein.

CLAIMS

1. A spore genetically modified with genetic code comprising at least one genetic construct encoding an antigen and a spore coat protein as a chimeric gene, said genetically modified spore having said antigen expressed as a fusion protein with said spore coat protein for use in oral or intranasal or rectal administration for therapeutic treatment.

2. A spore as claimed in Claim 1 characterised in that the spore is of Bacillus species.

3. A spore as claimed in Claim 1 or Claim 2 characterised in that the genetic construct comprises at least part of a spore coat protein gene and at least part of an antigen gene, in the form of a chimeric gene.

4. A spore as claimed in any one of the preceding Claims characterised in that the antigen gene is located at the 3' end of the spore coat protein gene.

5. A spore as claimed in any one of the preceding Claims characterised in that the genetic construct comprises a spore coat promoter at the 5' end of the chimeric gene.

6. A spore as claimed in any one of the preceding Claims characterised in that the antigen is at least one of tetanus toxin fragment C or labile toxin B subunit.

7. A spore as claimed in any one of the preceding Claims characterised in that the spore coat protein is selected from the group

consisting of *cotA, cotB, cotC, cotD, cotE, c otF, cotG, cotH, cotJA, cotJC, cotM, cotSA, cotS, cotT, cotV, cotW, cotX, cotY* and *cotZ*.

8. A spore as claimed in any one of the preceding Claims characterised in that the spore is heat inactivated so that in use it does not germinate into a vegetative cell.

9. A spore as defined in any one of the preceding Claims for use in the treatment of a medical condition.

10. A composition comprising at least two different spores as defined in any one of the preceding Claims characterised in that said at least two different spores express at least two different antigens.

11. A composition as defined in Claim 10 characterised in that the composition further comprises a pharmaceutically acceptable excipient or carrier.

12. A composition comprising a spore as defined in any one of claims 1 to 9 in association with a pharmaceutically acceptable excipient or carrier for use in oral or intranasal or rectal administration for therapeutic treatment.

13. A composition as defined in any one of Claims 10 to 12 for use in treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

14. Use of a spore as defined in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

15. A method of medical treatment, which method comprises the steps of

a) administering a spore as defined in any one of claims 1 to 9 to a human or animal in need of medical treatment by an oral, intra-nasal or rectal route;

b) said genetically modified spore eliciting an immune response for use in the prevention of a disease.

16. A method of producing a genetically modified spore, which method comprises the steps;

producing genetic code comprising at least one genetic construct encoding an antigen and a spore coat protein as a chimeric gene;

using said at least one genetic construct to transform a vegetative mother cell;

inducing said transformed mother cell to sporulate; and

isolating the resulting genetically modified spores.